Clinicopathologic Conference

Multiple Cerebral Emboli in a Young Man

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JEANNETTE J. TOWNSEND, MD: The patient, a 28-year-old man, had had generalized seizures for several years. He was apparently well until a week before his admission at the University of Utah Medical Center (UUMC). At that time the patient was admitted to a local hospital because of fever and dehydration due to vomiting and diarrhea. Evaluation revealed no abnormalities of the throat, a negative stool culture and normal chest x-ray film. During this week of hospital stay, he continued to have fevers, diarrhea, malaise and arthralgias. On the night before transfer, the patient was found to have acute aphasia with a right hemiparesis. A serum phenytoin concentration was 2.3 μg per ml and the phenobarbital level was 16 μg per ml. The clinical diagnosis was postictal paralysis, and phenytoin was intravenously administered. The patient was then transported to UUMC for further evaluation.

His medical history indicated that he was born prematurely with a birth weight of 2,041 grams (4 lb 8 oz). He was noted to be cyanotic in the neonatal period but was discharged home on the fifth postnatal day. He was a "slow learner" in school. His seizure disorder was fairly well controlled on a regimen of phenobarbital, phenytoin and carbamazepine. He had had hepatitis as a child with complete recovery. At age 17 he was treated for a bleeding peptic ulcer that resolved. At age 23 he was treated for hypertension. He had smoked two packs of cigarettes per day for the past ten years. He had a history of homosexuality. A test for the human immunodeficiency virus antibody one month before admission was negative. There was no history of head trauma, alcoholic intake or operations. There were no known allergies and no family history of thromboembolic disease, seizures or arthritis. Admission to UUMC a month before this admission for evaluation of his chronic seizures did not document any fevers, intestinal problems or arthralgias.

On arrival the patient was dysphasic and awake but not moving his right side. He was able to follow some simple commands with his left hand. Vital signs showed a temperature of 38.3°C (101.8°F), pulse 76 and regular, respirations 28, blood pressure 120/76 mm of mercury. He was tall and mildly obese, weighing 109 kg (240 lb). Head, eyes, ears, nose and throat examination showed a supple neck, mild pharyngeal erythema without exudate or adenopathy, normal ocular fundi and no evidence of trauma. There was no rash or adenopathy. Chest auscultation revealed diminished breath sounds in all fields and bibasilar rales. On cardiovascular examination there was no jugular venous distension but there were normal first and second heart sounds except for a question of a split S_1. There was no murmur, gallop or rub. There were no carotid bruits and both carotids had normal palpable pulses. His liver edge was palpable 3 cm below the right costal margin. The spleen was not enlarged and there were no abdominal masses or areas of tenderness. Results of a rectal examination were normal, including a negative test for occult blood in the stool. Genitalia were normal.

On neurologic examination he had a nonfluent severe dysphasia. When asked to show two fingers to the examiner, his best response consisted of lifting up his left arm. There was conjugate eye deviation to the left. Pupils were 5 mm, equal and reactive to light. There was pronounced right lower facial muscle weakness. Corneal reflexes were intact though slower on the right. Gag response was diminished but present. Motor examination revealed a substantial right hemiparesis and normal power in the left arm, hand and leg. He appeared to respond to pinprick stimuli in both arms and legs with purposeful withdrawal on his left side. Deep tendon reflexes were 1/4 and symmetric in the upper extremities and 2/4 and symmetric in the lower extremities. Plantar responses were present and flexor bilaterally.

Laboratory studies on admission elicited the following values: serum sodium 138 mEq per liter, potassium 3.7 mEq per liter and glucose 104 mg per dl; alkaline phosphatase 146, lactic dehydrogenase 172, aspartate aminotransferase 33, alanine aminotransferase 56 and γ-glutamyltransferase 203 IU per liter; urate 5.6, calcium 8.6 and phosphorus 2.8 mg per dl; total protein 5.6 and albumin 3.1 grams per dl; cholesterol 147 and total bilirubin 0.5 mg per dl, and magnesium 2.0 mEq per liter. A complete blood count showed the following: leukocyte count 6,300 per μl with 73% polymorphonuclear neutrophils, 3% bands, 17% lymphocytes, 3% monocytes and 4% eosinophils; hemoglobin 14.9 grams per dl; hematocrit 44%; normal indices, and platelets 229,000 per μl. Prothrombin time was 15.3 seconds with control 12.3 seconds. Partial thromboplastin time was 34 seconds with control 37 seconds. Westergren sedimentation rate was 5 mm per hour. A rapid plasma reagin test was nonreactive. The antinuclear antibody test was negative at less than 1:20. A drug screen revealed a phenobarbital concentration of 16 μg per ml, a carbamazepine concentration of 1.2 μg per ml and a phenytoin concentration of 7.0 μg per ml. Analysis of a urine specimen obtained after placement of an indwelling catheter showed a specific gravity of 1.029, pH 5, trace protein, trace glucose, moderate blood, no ketones, bilirubin or nitrites.

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography
2-D = two-dimensional
ECG = electrocardiogram
P_{CO_2} = partial pressure of carbon dioxide
P_{O_2} = partial pressure of oxygen
UUMC = University of Utah Medical Center

The microscopic examination showed 20 to 50 erythrocytes per high-power field and 10 to 20 leukocytes per high-power field, no bacteria, casts or crystals and 3+ mucus. Arterial blood gas determinations done while the patient was receiving 6 liters per minute of oxygen showed pH 7.49, partial oxygen pressure (P_{O_2}) 112 torr, partial carbon dioxide pressure (P_{CO_2}) 35 torr and O_2 saturation at 94%.

A nonenhanced computed tomographic (CT) scan of the brain revealed a low-density lesion involving most of the left middle cerebral artery distribution without areas of hemorrhage (Figure 1). There was obliteration of the left sylvian fissure. A portable x-ray film of the chest showed a questionable left lower lobe infiltrate, but no other abnormalities. An electrocardiogram (ECG) showed sinus bradycardia with 58 beats per minute, a PR interval of 0.12 seconds, QRS 0.08 seconds, QT 0.52 seconds and axis 0°. There were large T waves in leads II and V_2 through V_4.

The cerebrospinal fluid (CSF) examination showed an opening pressure of 240 mm water with 1 leukocyte and 1 erythrocyte per μl and no xanthochromia. The protein level was 36 mg per dl and the glucose 69 mg per dl. A Gram's stain and bacterial culture were negative.

The patient was treated with oxygen by nasal cannula, intravenous administration of phenytoin and phenobarbital and carbamazepine given per nasogastric tube. A regimen of high-dose dexamethasone was begun in an attempt to minimize brain swelling. On the second hospital day, cerebral angiography revealed occlusion of the left internal carotid artery with a narrowing beginning 1 cm distal to its origin and gradually tapering over several centimeters to complete occlusion at about the level of C1-2 (Figure 2). There was no evidence for collateral flow from the external carotid to intracerebral vessels. The right internal carotid and right vertebral arteries were normal. Both anterior cerebral arteries were perfused by the right internal carotid. No cross filling to the left middle cerebral artery was seen.

The angiogram was felt to be most consistent with a carotid dissection. Heparin therapy was begun with an intravenous bolus followed by continuous infusion. A CT scan taken before initiation of this therapy again showed no hemorrhage but continued mass effect with obliteration of the sylvian fissure. There was no known history of recent head or neck trauma or of chiropractic manipulation.

Because of the possibility of pneumonia on admission, the patient was given clindamycin parenterally. Fevers abated within 48 hours, and he remained afebrile until the seventh hospital day when a fever of 38.8°C (101.8°F) developed. Repeat chest x-ray film showed resolution of the infiltrate and no new infiltrates. Blood cultures were negative. Culture of a urine specimen from an indwelling catheter grew 10^5 colonies per ml each of *Klebsiella, Escherichia coli* and *Proteus*. He was given gentamicin sulfate intravenously, but continued to have intermittent diarrhea. The clindamycin therapy was discontinued. Stool culture, examination for ova and parasites and a *Clostridium difficile* toxin assay were all negative.

Heparin resistance was noted. After numerous heparin boluses and increasing infusion rates, the patient finally had a

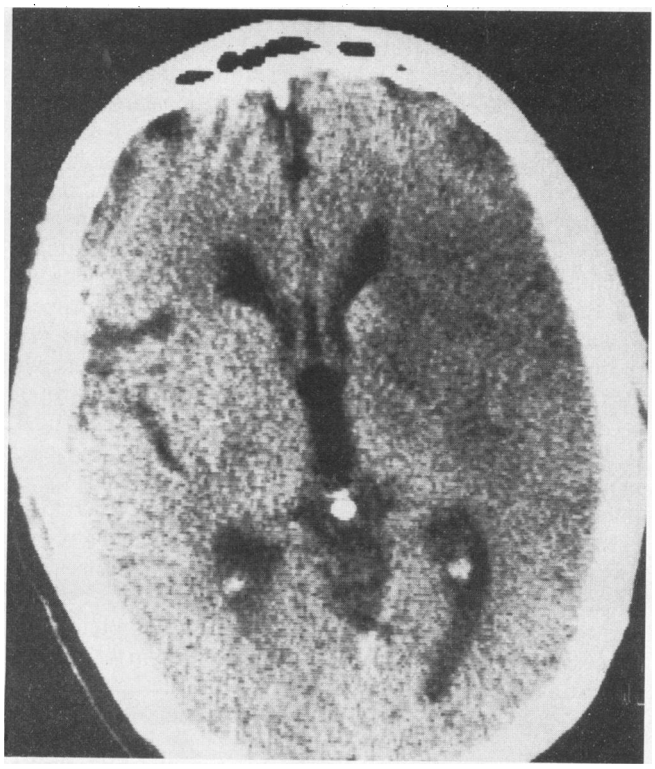

Figure 1.—An unenhanced computed tomographic scan shows a nonhemorrhagic low-density lesion on the left.

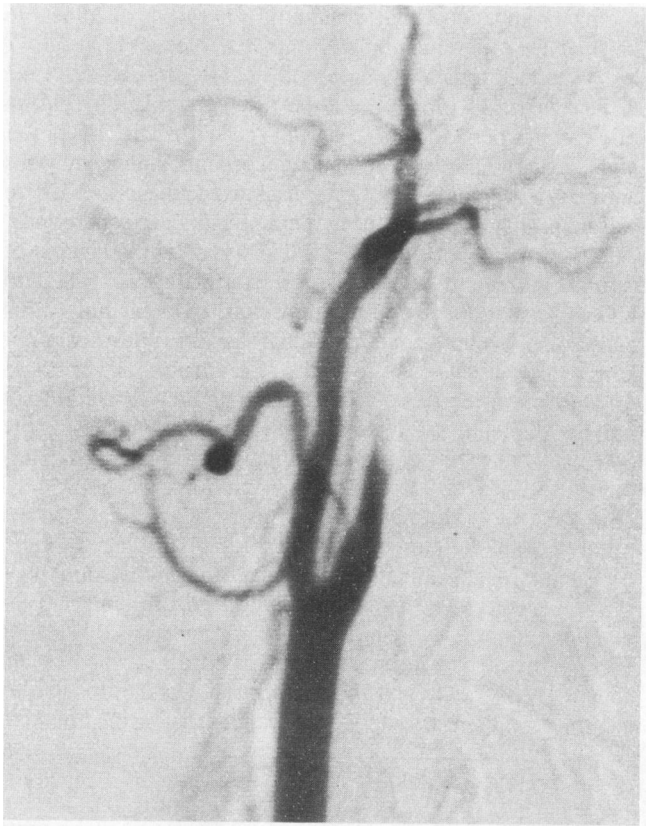

Figure 2.—An angiogram shows tapered occlusion of the left internal carotid artery.

partial thromboplastin time of 78 seconds with a control of 36 seconds on the 12th hospital day while receiving a heparin infusion at a rate of 2,500 units per hour.

The patient was obtunded on the second and third hospital days. He awoke on the fourth hospital day and remained conscious for the next ten days. There was no improvement in his language comprehension or production. Reflexes remained present on the right, but no motor responses could be elicited on that side. His left gaze preference diminished.

On the 13th hospital day, the patient was found cyanotic with bilateral upper extremity clonic activity followed by tonic rigidity of all extremities. Arterial blood gas determinations made after the event showed Po_2 57 torr, Pco_2 32 torr and pH 7.47 with the patient breathing room air. Electrolytes, glucose, calcium and magnesium levels were normal. Serum drug concentrations showed phenytoin 7.3 μg per ml, phenobarbital 24 and carbamazepine 3.5 mg per ml. His temperature was 38.8°C and a chest x-ray film showed new infiltrates at both bases. The patient did not regain consciousness. He had intermittent decerebrate posturing on the left side with decorticate posturing on the right. Pupils were 5 mm and reactive to light. Corneal and oculovestibular reflexes were present. Decerebrate posturing on the left was present with ipsilateral noxious stimuli. Bilateral extensor plantar responses were noted.

The patient was placed on a ventilator for respiratory support though spontaneous breathing persisted. A repeat CT scan done at this time showed no hemorrhage. A repeat study two days later revealed new low-density foci in the left occipital and basal ganglia region and in the region of the right basal ganglia (Figure 3).

Heparin therapy was discontinued and dexamethasone therapy resumed. A trial of mannitol produced no neurologic improvement. An echocardiogram showed normal left ventricular chamber size, wall thickness and motion. The other cardiac chambers and great vessels were normal. No abnormalities of any cardiac valves were found. Doppler recordings showed no regurgitation. No source for emboli was found. Two days after the heparin therapy was discontinued, protein C, protein S and antithrombin III levels were measured, with no evidence of deficiency found.

The patient's condition was unchanged on the 19th hospital day. Ventilatory support was withdrawn, and he died on the 20th hospital day.

Discussion

MARK P. NESPECA, MD: The annual reported incidence for stroke in persons younger than 35 years in the United States has varied from 0 to 8 per 100,000.[1] Strokes in the young provide diagnostic and therapeutic dilemmas, as shown by the case reported herein. In this age group, nonhemorrhagic stroke is usually associated with a predisposing systemic disease affecting the heart or the extracranial or intracranial vascular system. Table 1 provides a list of systemic diseases to consider in a young person with an ischemic cerebral infarction. A few disease states are manifested only by cerebrovascular pathologic lesions (Table 2).

His history and findings on physical examination exclude several possibilities such as cyanotic congenital heart disease, a cardiac operation, sickle cell anemia, hypertension, diabetes mellitus, nephrotic syndrome, phakomatoses, homocystinuria (95% have dislocated lens), steroid therapy, fat embolism and mastoiditis. Laboratory studies either eliminate or reduce the likelihood of his stroke being related to leukemia, thrombocytosis, polycythemia, coagulation factor deficiencies, hypercoagulable state, cardiac dysrhythmia, nephrotic syndrome or meningitis. Cerebrospinal fluid findings provided strong evidence against neurovascular syphilis, which in recent years may be the most common form of neurosyphilis.[2] It is always hard to be certain that illicit drugs are not part of the clinical spectrum. The history and physical examination findings did not suggest this, and the fact that he was in his local hospital for a week before his stroke should have reduced access to such agents.

Severe dysphasia prevented the patient from giving an extensive history, and thus little was known about various aspects of his recent illness, except that fever, diarrhea and arthralgias of recent onset were present. He had not had these symptoms one month before admission when he was evaluated for chronic seizures. Had these intestinal complaints been more chronic, one could implicate inflammatory bowel disease predisposing him to stroke.[3] His tall stature, mild obesity and lack of occult blood in the stool argue against his having Crohn's disease or chronic ulcerative colitis. Acute gastroenteritis with dehydration is associated with cerebral venous or dural sinus thrombosis and could have caused the patient's symptoms. The CT scan, however, documented arterial occlusion as opposed to venous occlusion, and the unenhanced CT scan did not show the zones of patchy increased density within zones of low attenuation, cerebral hemorrhage or gyral enhancement commonly associated with cortical venous thrombosis.[4]

The CT evidence of arterial disease leads us to consider the disorders listed in Table 2. A recent study found athero-

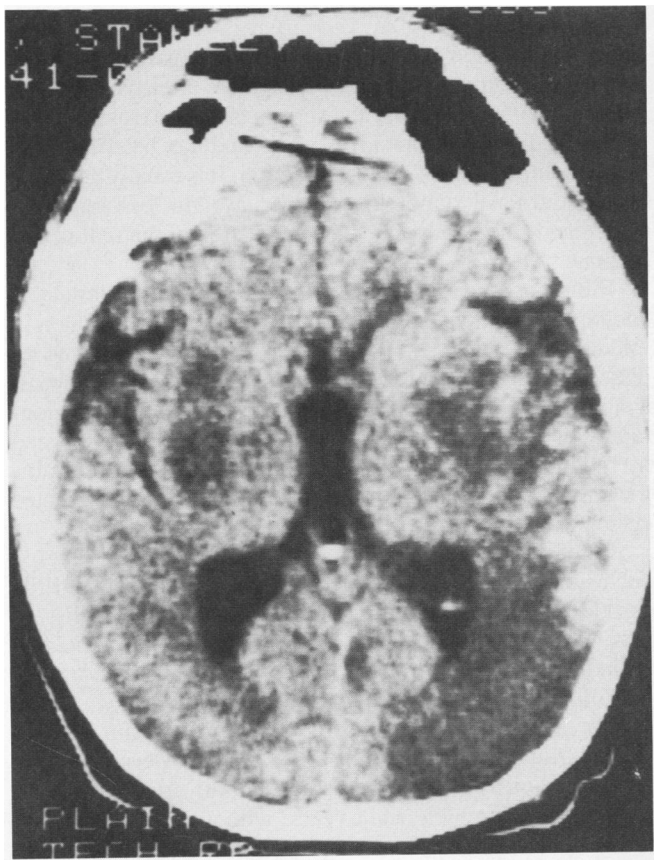

Figure 3.—A final computed tomographic scan shows new low-density lesions bilaterally.

sclerosis to be the cause of nonhemorrhagic cerebral infarction in 27% of 144 patients aged 15 to 45 years.[5] All but three of these had definable risk factors such as cigarette smoking, hypertension, diabetes mellitus or hyperlipidemia. This patient did have a history of cigarette smoking and transient hypertension, but there was no evidence of any atherosclerotic changes in the right carotid or cerebral circulation to suggest that this was the cause of his stroke.

Traumatic causes of nonhemorrhagic stroke were unlikely, although recent neck trauma could not be ruled out. There was no evidence on examination of intraoral injury, and cervical spine trauma would be more likely to compromise the posterior cerebral circulation. The patient clearly had anterior circulation ischemia as seen with carotid dissection, which can occur either with or without trauma.

Granulomatous angiitis is an uncommon disease that can occur at any age and has no particular sex or age predilection. Symptoms usually consist of a subacute encephalopathy with headache, nausea, vomiting and alteration of mental state. A fourth of patients have fever, chills and weight loss and in most, focal signs such as hemiparesis, dysphasia, seizures or visual loss ultimately develop. Unlike our patient, however, 80% of patients have an elevated CSF protein level and 90% have a CSF pleocytosis ranging as high as 180 cells per μl with a lymphocytic predominance.[6] Angiography shows segmental narrowing and irregularity of small distal vessels. Only 50% of patients show angiographic abnormalities. Large vessels may be involved but this is uncommon. Slightly more than half of the patients have a mild to moderate elevation in the sedimentation rate. Associations with Hodgkin's disease, *Mycoplasma* and herpes zoster have been reported but arthralgias and diarrhea are not seen.[7]

Cranial arteritis (giant cell arteritis) can be eliminated from consideration primarily by virtue of the patient's age and the normal sedimentation rate. Takayasu's arteritis (pulseless disease) involves the aorta and vessels that arise from its arch. This is a disease of unknown cause and has been reported primarily in women of Asian extraction. It is usually preceded by constitutional symptoms of fever, weight loss and night sweats and also has an associated elevation of the sedimentation rate.

Fibromuscular dysplasia of the internal carotid artery is another uncommon cause of stroke. This is more common in middle-aged women. The vessel can undergo spontaneous dissection, aneurysmal formation or thromboembolic events leading to cerebral infarction. Diagnosis is made by angiography, which can show alternating zones of widening and narrowing of the artery (string of beads), unifocal or multifocal tubular stenosis or aneurysmal dilatation of the affected vessel.

Cerebral angiography in this patient revealed a tapered occlusion of the left internal carotid artery that spared the carotid bulb. This finding is most typical of carotid dissection.[8-10] Although fibromuscular dysplasia is often associated with dissection, there were no angiographic features suggestive of fibromuscular dysplasia in the contralateral carotid system. In addition, the results of the angiogram did not suggest granulomatous angiitis or Takayasu's arteritis.

Dissections of the extracranial carotid artery are most common in the middle adult years, with a peak incidence at age 45. They may occur at any age and have no definable gender predilection. This condition often appears spontaneously in otherwise healthy persons, but may be associated with underlying arteriopathy or various types of trauma. Cystic medial degeneration was often reported in early autopsy studies but examination of surgical specimens has shown dissections occurring in arteries that are either microscopically normal or show only disorganized, fragmented elastic fibers.[11] Other arteriopathies associated with dissection include fibromuscular dysplasia, Marfan's syndrome, atherosclerosis, syphilitic arteritis and hypertension. Hyper-

TABLE 1.—*Systemic Conditions Predisposing to Ischemic Stroke in Young Patients*

Cardiac Disease
Cyanotic congenital heart disease
Rheumatic heart disease
Dysrhythmias
Infective endocarditis
Other valvular disorders, such as mitral valve prolapse
Atrial myxoma
Cardiac operation
Myocarditis
Infection
Meningovascular syphilis
Bacterial or fungal meningitis
Viral encephalitis or meningitis
Gastroenteritis with dehydration
Mastoiditis
Hematologic and Neoplastic Diseases
Sickle cell anemia
Leukemia
Coagulation factor abnormalities, such as antithrombin III, protein C or protein S deficiency
Thrombocytosis
Metastatic neoplasms
Polycythemia
Trauma
Intraoral trauma to carotid artery
Fat embolization with long bone fracture
Carotid dissection
Cervical spine trauma with vertebral artery trauma
Miscellaneous
Systemic lupus erythematosus
Periarteritis nodosa
Hypertension
Diabetes mellitus
Nephrotic syndrome
Inflammatory bowel disease
Phakomatoses—neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis
Homocystinuria
Steroid therapy
Oral contraceptives
Illicit drugs—amphetamines, phencyclidine, LSD, "lookalikes," heroin
Local mass effect of skull-based tumor, retropharyngeal abscess or brain tumor

TABLE 2.—*Primary Disease of the Cerebral Vasculature*

Fibromuscular dysplasia
Carotid dissection, nontraumatic
Takayasu's arteritis
Cranial (temporal) arteritis
Granulomatous angiitis
Moyamoya disease
Atherosclerosis

extension and rotational injury to the neck along with blunt trauma and penetrating wounds have all been associated with dissection. It is interesting to note that dissection can occur after trivial trauma such as coughing, blowing the nose or brushing the teeth or with common sports such as tennis, volleyball or bowling. Presentation with an initial massive stroke, however, is uncommon with dissection, probably occurring in no more than 5% of cases. Recurrent transient ischemic attacks are more common after dissection. Most patients have associated severe headache or neck pain, and many will have pulsatile tinnitus or an ipsilateral Horner's syndrome. Transient monocular blindness is also commonly reported.

Most authors recommend anticoagulant therapy in patients with carotid dissection to minimize the likelihood of secondary thrombotic or embolic infarction. Heparin therapy was begun in this patient, and his hospital course was marked by intermittent fevers and diarrhea, heparin resistance and resolution of the infiltrates on the chest radiograph. When adequately anticoagulated, however, he had acute neurologic deterioration due to new cerebral infarctions in the right and left basal ganglia and left occipital lobe. The bilateral lesions virtually eliminated carotid dissection as the source of his cerebral disease.

We are thus left with the task of explaining multiple nonhemorrhagic infarctions occurring in small and large vessels in both the middle and posterior cerebral circulations. Arthralgias and gastrointestinal symptoms commonly occur along with fever and rash in patients with polyarteritis nodosa, but signs and symptoms of peripheral neuropathy are much more common (60% to 70% have neuropathies) than cerebral infarction (less than 10%) and tend to precede the latter.[6] The other possible vasculitides have already been discussed.

Bilateral lesions without evidence of vasculitis suggest embolic events and compel us to take a closer look at the heart in this young man. Advances in cardiac, cerebral and vascular imaging have shown that about 25% of strokes are caused by heart lesions. In patients younger than 45 years, cardiac pathology may be responsible for as many as 50% of nonhemorrhagic strokes.[12] In this patient, results of the admission evaluation did not point toward cardiac pathology, as the cardiac examination showed no abnormalities. There was a normal cardiac silhouette on chest film, and an ECG showed only mild sinus bradycardia. No dysrhythmias or hypotension was noted in his first few days in an intensive care unit with frequent monitoring. It was only after the appearance of subsequent infarction that a two-dimensional (2-D) echocardiogram was done. No evidence of mitral valve prolapse or atrial myxoma was found. The most common angiographic abnormality in young patients with mitral valve prolapse and cerebral ischemic symptoms is branch occlusion, followed by middle cerebral artery occlusion and then internal carotid artery occlusion.[12,13] Our patient did not have evidence of branch occlusion but rather a tapered occlusion of the internal carotid. A tapered occlusion that spares the carotid bulb, although common in carotid dissection, could conceivably be mimicked by embolic or thrombotic disease.[8,9]

Acute viral myocarditis is often associated with fever and may be associated with other systemic symptoms. Signs of congestive heart failure or dysrhythmias or both are usually present, especially if cardiac dysfunction is severe enough to provide a locus for the formation of mural thrombi. A normal echocardiogram showing no abnormalities in wall motion provides compelling evidence against a severe viral myocarditis, but does not exclude a milder form of involvement.

The arthralgias and fever suggest the diagnosis of acute rheumatic fever with associated carditis. It is hard to explain his diarrhea on this basis, but the persistence of the diarrhea may have been due to the continuous antibiotic therapy after his admission. Beyond a history of arthralgias and evidence of fever, we have little else to support a diagnosis of acute rheumatic fever. There was no previous history of rheumatic heart disease or recent scarlet fever. On physical examination he had no evidence of polyarthritis, cardiac murmur, chorea, erythema marginatum or subcutaneous nodules. His throat culture was negative at the referring hospital. The sedimentation rate was normal and the PR interval was not prolonged. The normal echocardiogram argues against active rheumatic carditis.

Finally, we must consider infective endocarditis as the cause of this clinical spectrum.[14,15] This would still not explain his diarrhea. He had no known history or evidence of congenital or acquired cardiac disease predisposing him to endocarditis. Neither did the patient have an elevated sedimentation rate, anemia, abnormal urinary sediment or peripheral signs of embolization outside the central nervous system. He did have microscopic hematuria that could have been due to renal infarcts.

Fever, arthralgias and multiple cerebral emboli in a young patient, however, force us to consider endocarditis despite the above considerations. The patient had at least three sets of blood cultures done, with at least one set before antibiotic therapy. The use of clindamycin and gentamicin may have inhibited bacterial growth in subsequent cultures, and 15% of patients with bacterial endocarditis may have a negative first blood culture.

A normal 2-D echocardiogram does not exclude endocarditis. About 20% to 50% of patients with infective endocarditis may fail to show vegetations. The minimum detectable size of vegetations is usually 2 mm, and this increases with

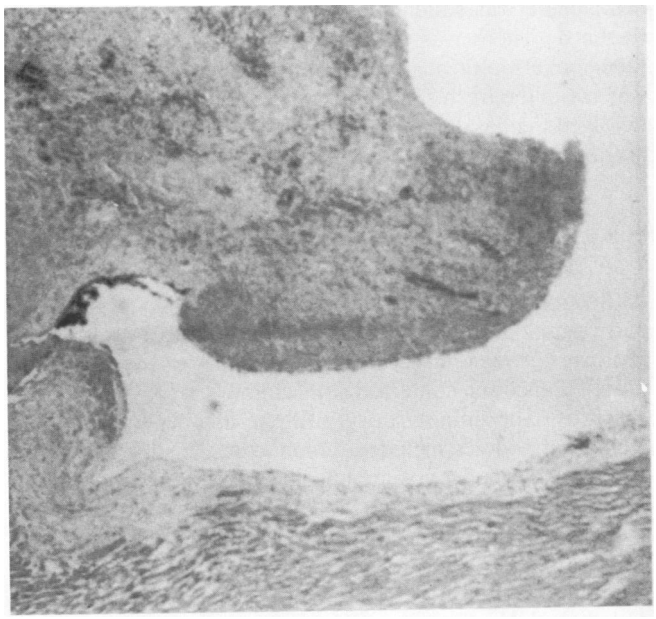

Figure 4.—The low-power micrograph shows adherent thrombus in the left ventricle. The myocardium can be seen at the bottom of the picture (hematoxylin-eosin, × 65).

increasing distance beyond 7 cm from the transducer.[16] Limitations of the echocardiogram in defining other cardiac sources of emboli have been shown by various studies.[17] The sensitivity for detecting mural thrombi after myocardial infarction varies from 72% to 95%. In one study the smallest detected thrombus was 2.0 by 2.0 by 1.5 mm.[18] We are thus unable to exclude a cardiac source of emboli on the basis of a normal 2-D echocardiogram.

It is clear from the foregoing discussion that this clinical state of fever, arthralgias, diarrhea and multiple nonhemorrhagic cerebral infarctions with no abnormalities found on a cardiac examination and normal sedimentation rate, ECG and 2-D echocardiogram is difficult to reconcile with the disorders discussed above. Multiple cerebral infarctions, however, compel us to implicate primary cardiac disease, and the most likely cardiac disease causing multiple emboli in a young man with a normal echocardiogram would be infective endocarditis. This would explain his fever and arthralgias. Secondary consideration would be given to acute rheumatic fever without the usual associated features and viral myocarditis, either of which could cause associated mural thrombi undetected by echocardiography.

Pathology

DR TOWNSEND: The autopsy was limited to examining the heart, liver, the bifurcation of the internal and external carotid artery on the left and the brain. Sections were taken but the organs were returned to the body.

The heart weighed 580 grams. The external surface was normal and there were no abnormalities of the valves. An adherent thrombus measuring 1.5 by 0.8 by 0.3 cm was found at the apex of the left ventricle (Figure 4). The myocardium grossly appeared normal. The other chambers were free of thrombus and the right ventricle showed mild hypertrophy.

At the bifurcation of the left internal and external carotid artery, the internal carotid artery was distended with a firm clot. This clot extended to involve both the left anterior and left middle cerebral arteries within the cranial vault.

The brain weighed 1,700 grams. The surface of the left hemisphere was softened and discolored, and the gyri were flattened. There was no evidence of uncal herniation, but moderate atrophy was present in the frontal lobes. The brain was cut in the fresh state, and the area of softening on the left involved the basal ganglia and the frontal, parietal, temporal and occipital lobes in the distribution of the left anterior, middle and posterior cerebral arteries. A discolored softened area was also found in the right putamen measuring 2 by 3 cm. The ventricles were enlarged. The cerebellum and brain stem showed no abnormalities.

Sections of the heart showed a diffuse myocarditis with perivascular chronic inflammatory cells and areas of fibrinous necrosis between muscle bundles. These areas were nodular in appearance and contained Anitschkow's myocytes (Figures 5 and 6). The inflammatory infiltrate associated with these interstitial nodules included lymphocytes, histiocytes, occasional plasma cells, eosinophils and polymorphonuclear leukocytes. These cellular Aschoff bodies represent the classic proliferative stage seen in the heart of patients who have acute rheumatic fever with carditis. The apical thrombus showed beginning organization and adherence to the endocardium. The thrombus was composed of platelets, fibrin and occasional mononuclear cells. No organisms were found on special stains.

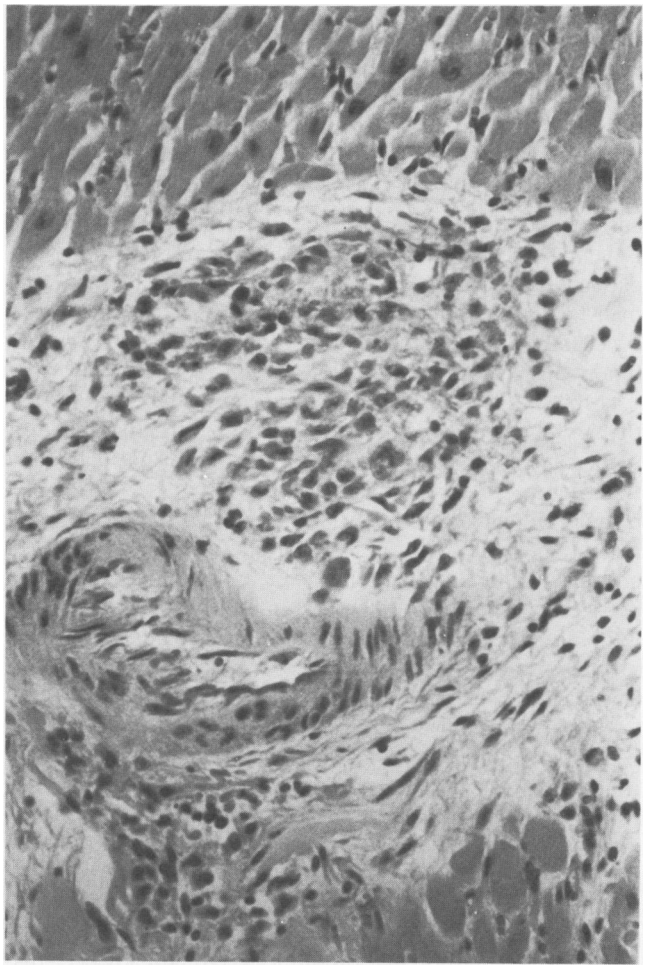

Figure 5.—Nodular accumulation of mononuclear cells forms the Aschoff body adjacent to a vessel in the interstitium (hematoxylin-eosin, × 200).

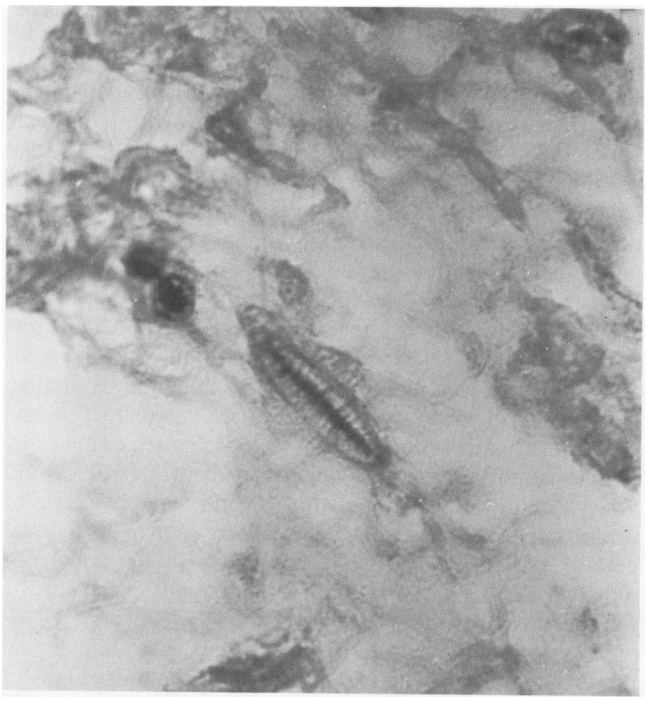

Figure 6.—The micrograph shows a typical Anitschkow's myocyte with a caterpillar-like shape to the nucleus (hematoxylin-eosin, × 450).

Sections of the left internal carotid artery revealed an adherent thrombus composed of fibrin, platelets and scattered mononuclear cells. Sections of the softened areas of the left cerebral hemisphere showed focal areas of necrosis with macrophage response and surrounding scattered astrocytes. The lesion in the right putamen was more recent with eosinophilic shrunken neurons and no macrophage response.

These gross and microscopic findings confirmed a diagnosis of acute rheumatic myocarditis with a mural thrombus of the left ventricle. This led to both left and right carotid embolization with secondary infarction of the brain.

This case was a diagnostic problem for the clinicians. Although the clinical course suggested the heart as the source of the emboli, the studies done to evaluate cardiac disease did not substantiate an obvious heart lesion. Rheumatic fever has been an elusive diagnosis in the past and still presents diagnostic difficulties.[19] This is especially true in an era when acute rheumatic fever continues to decrease in incidence in the United States.[20,21] It is interesting to note that there has been a recent increase in the incidence of rheumatic fever in the state of Utah. Although this patient had two of the minor criteria for rheumatic fever—that is, arthralgias and fever—the carditis as one of the major criteria was not proved until after death. Migrating arthritis with swelling and inflammation of the joints was not recorded in this patient, although this is a common manifestation of the disease. The other major criteria—erythema marginatum, subcutaneous nodules and chorea—are less common and the last two are usually seen in children. This case does show that extensive interstitial myocardial disease may be present without detectable electrical or echocardiographic abnormalities. The early disease in this patient, although widespread, had not affected the ability of the heart to function. There was no evidence at autopsy of cardiac failure. His death could have been due to an acute arrhythmia but was most likely due to the cerebral infarctions with secondary brain swelling. The inability of the two-dimensional echocardiogram to show the apical thrombus in the left ventricle is significant. It is known that echocardiograms may miss mural thrombi simply because of their small size, but perhaps the location and the ability to separate the thrombus, especially at the apex, from the heart wall play an important role in their detection.[18] The thrombus in this case was relatively large and must have been obscured by the apical heart muscle. It is unfortunate that the use of heparin, which is the treatment of choice in patients with mural thrombi, did not prevent further embolization.

This case again emphasizes the need to consider the diagnosis of acute rheumatic fever in younger patients presenting with embolic phenomena after the more common causes of emboli have been eliminated.[22]

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